ORIGINAL ARTICLE
Iran J Allergy Asthma Immunol
December 2022; 21(6):704-710.
Doi: 10.18502/ijaai.v21i6.11531

Effect of Temperature and Humidity on the Allegro-inflammatory Factors and Allergic Rhinitis-related Behavior

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Received: 14 May 2022; Received in revised form: 25 May 2022; Accepted: 13 June 2022

ABSTRACT

Allergic rhinitis (AR) is an allergic disease induced by the T helper 2 (T_H2) lymphocyte immune response, where its mediators are the primary cause of clinical symptoms. Environmental factors are the primary determinants of the allergic response in genetically susceptible individuals. This study investigates the effects of climate conditions (warm, cold, humid, and dry) on allergic rhinitis.

AR models were created in mice under 4 different conditions. We investigated AR-related behavior (sneezing and nose rubbing), as well as total immunoglobulin E (IgE), histamine, interleukin-4 (IL-4), leukotriene (LT) B4 and LTC4 levels, and gene expression of *CysLT1R*, *HRH1*, and *MUC5a*.

Nose rubbing, histamine levels, and the expression of *MUC5a* and *HRH1* were increased in AR models in cold conditions, and sneezing was increased in AR models kept in dry conditions. LTB4 and LTC4 levels and the expression of *CysLT1R* in AR models kept in a wet environment also significantly increased compared with the control group. The levels of total IgE and IL-4 showed no significant changes.

Air temperature and humidity affect AR pathophysiology, and weather conditions can be essential in controlling AR.

Keywords: Gene expression; Histamine; Leukotrienes; Sneezing

INTRODUCTION

Allergies are a significant global health burden, particularly in industrialized nations. Allergic rhinitis (AR) is initiated by interleukin (IL)-4, Ig (immunoglobulin) E-bound Fc epsilon receptors (FcεRs) on the surface of mast cells, and allergo-inflammatory mediators in immediate and late phases. Dendritic cells take up and transport allergens to the lymph nodes. Cross-talk between T lymphocytes and dendritic cells activates allergen-specific T and B cells (type 2 lymphocytes). In predisposed individuals, IL-4 released from T_H2 stimulates B cells to undergo IgE class switching. IgE binds to Fcε-receptors with high

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affinity on mast cells and basophils (sensitization phase). When allergens reenter the body following this phase, they crosslink IgE attached to mast cells, prompting rapid degranulation and mediator release. These mediators are the primary cause of clinical symptoms and include histamine, serotonin, eicosanoids, cytokines, chemokines, tryptase, and leukotrienes. Environmental factors are the primary causes of allergy responses in genetically susceptible people.[1-3] Depending on where they reside, people are exposed to warm to subfreezing temperatures and dry or humid weather conditions. Cold or dry air produces respiratory symptoms and may contribute to AR.[4]

AR is an upper-airway disease characterized by nasal congestion, rhinorrhea, itching in the nose, intermittent or persistent sneezing, and cough. In AR, the inflammatory response is divided into two phases: early and late.[5] This study investigates the effect of warm, cold, humid, and dry air conditions on the gene expression of allegro-inflammatory–associated genes in a mouse model of allergic rhinitis.

MATERIALS AND METHODS

AR Model Producing and Groups

AR mouse models were created in 25 mature[7-8] weeks old) male BALB/c mice through sensitization and challenge with ovalbumin, according to the method described by Athari et al.[6] The mice were divided into 5 groups with 5 mice in each group and housed in different environmental settings: standard (AR), dry (AR-D), humid (AR-H) [80±5% humidity], cold (AR-C), and warm (AR-W) [32±2°C]. The animals were euthanized with CO_2 on day 31, and blood and nasal lavage fluid (NLf) samples were obtained.

AR-related Behavior

On day 30, sneezing and nose rubbing were investigated by counting the episodes every 15 min after each intranasal ovalbumin challenge.

NLf Collection

NLf samples were collected after anesthesia with lidocaine and xylazine; a catheter was guided into the nasopharynx of the mice. Nasal passages were gently perfused with 1 mL of phosphate-buffered saline, and NLf was collected. It was then centrifuged to separate cells from the supernatant.

Serum Biofactors

After separating the serum from blood samples, enzyme-linked immunosorbent assay kits (Biocompare, USA) were used to measure the levels of total IgE, histamine, IL-4, LTB4, and LTC4 in the serum.

Real-time PCR

Quantitative real-time PCR was used to determine *CysLT1R*, *HRH1*, and *MUC5a* gene expression (Qiagen, Germany). NLf-derived cells were used for RNA extraction. cDNA was synthesized, and gene expression was studied using specific primers (Supplementary Table).

Statistical Analysis

The statistical analysis was performed using SPSS Version 20.0 using the one-way analysis of variance (with Tukey's post hoc test). The data are presented as mean±SD. *p* values less than 0.05 were considered statistically significant.

RESULTS

AR-related Behaviors

Nose rubbing and sneezing in mice were considered behaviors representing AR symptoms in humans. Figure 1 depicts the comparison of the behaviors in the different groups. Nose rubbing was significantly increased in the AR-C group (22±1) compared with the AR group (17±1), and sneezing was significantly increased in the AR-D group (31±2) compared with the AR group (25±1).

Total IgE

The serum level of total IgE showed no significant difference in the AR group (2687±314) compared with the AR-C, AR-W, AR-H, or AR-D groups (2658±290, 2701±269, 2711±294, and 2695±425 ng/mL, respectively) (Figure 2A).

Interleukin-4

The IL-4 levels in NLf of the AR group (96±15 pg/mL) showed no significant difference compared with the AR-C, AR-W, AR-H, or AR-D groups (90±17, 98±14, 94±18, and 99±17 pg/mL, respectively) (Figure 2B).

Leukotrienes

The levels of LTB4 and LTC4 in the serum significantly increased in the AR-W group (159±14 and *398*±59 pg/mL, respectively) compared to the AR group (108±14 and *259*±48 pg/mL, respectively) (Figure 3A).

Histamine

Histamine levels in the serum significantly increased in the AR-C group (743±24 ng/mL) compared with the AR group (598±28 ng/mL). The other groups showed no significant differences compared with the AR group (Figure 3B).

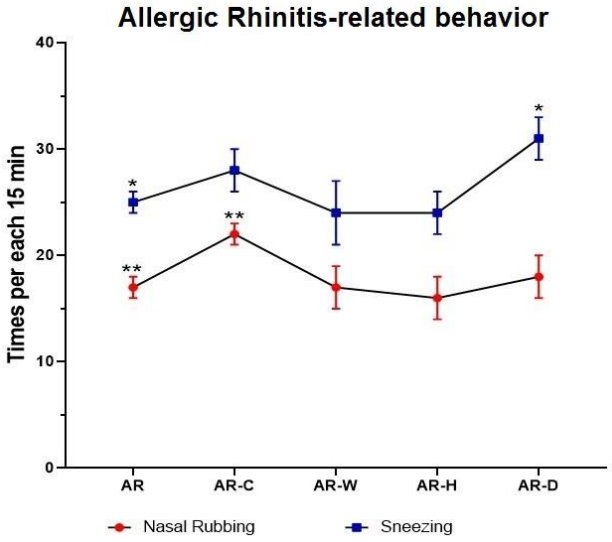

Figure 1. Allergic rhinitis (AR)-related behavior. Nose rubbing and sneezing were observed in all groups (standard (AR), dry (AR-D), humid (AR-H) [80±5% humidity], cold (AR-C), and warm (AR-W) [32±2°C]). Differences have been shown betwwen the test groups and standard group. *p<0.05, **p<0.01

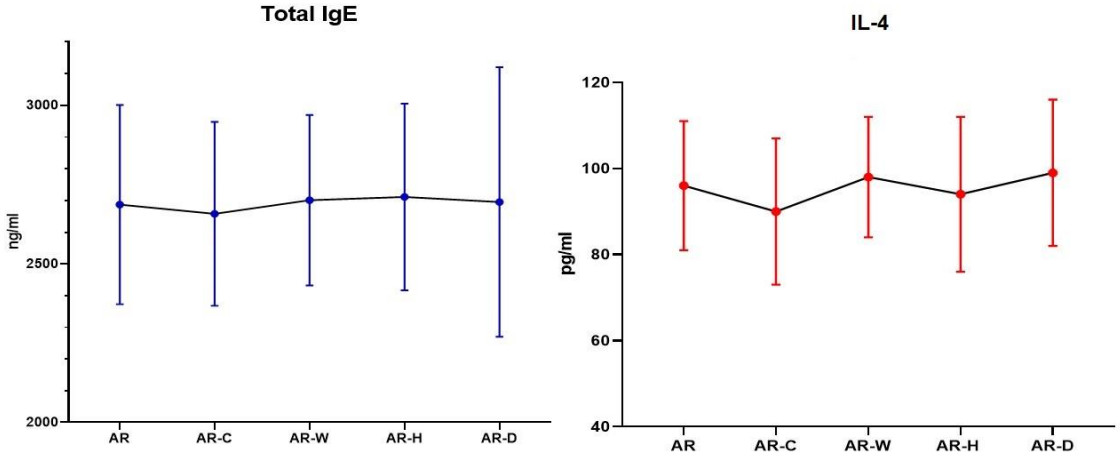

Figure 2. Total serum immunoglobulin E (IgE) and nasal lavage fluid interleukin-4 (IL-4) levels were measured using the enzyme-linked immunosorbent assay in all groups standard (AR), dry (AR-D), humid (AR-H) [80±5% humidity], cold (AR-C), and warm (AR-W) [32±2°C]..

Gene Expression

The gene expression of *MUC5a* and *HRH1* significantly increased in the AR-C group (29.5±1.4 and 9.5±0.8 relative expressions, respectively) compared with the AR group (17±1.5 and 3.4±0.4 relative expressions, respectively). The gene expression of *CysLT1R* significantly increased in the AR-W group (5.9±0.5 relative expression) compared with the AR group (3.1±0.6 relative expression) (Figure 4).

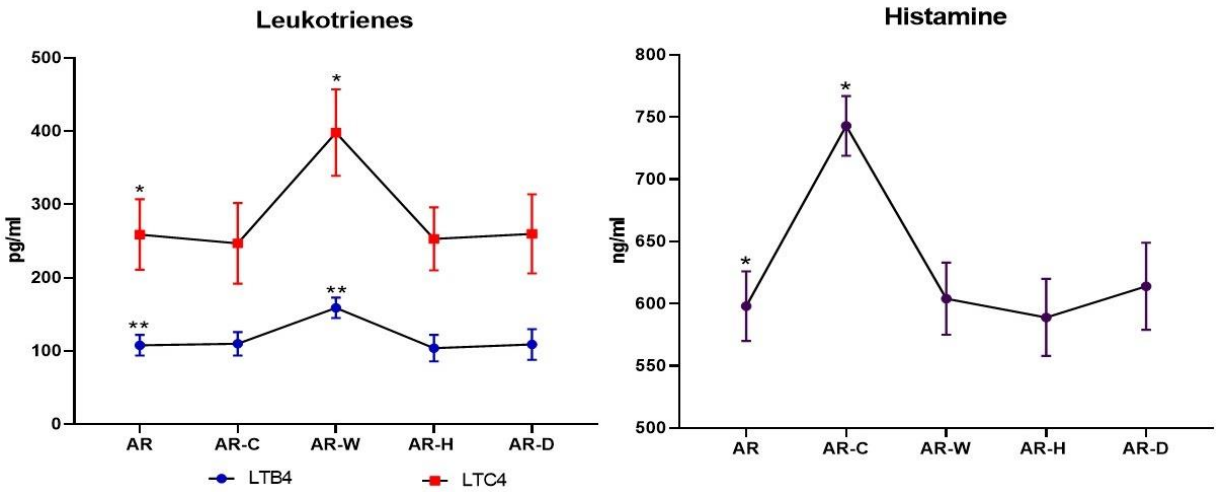

Figure 3. Levels of histamine, LTB4, and LTC4 in the serum of animals categorized in 5 groups (standard (AR), dry (AR-D), humid (AR-H) [80±5% humidity], cold (AR-C), and warm (AR-W) [32±2°C]). Differences have been shown betwwen the test groups and standard group. *p<0.05, **p<0.01

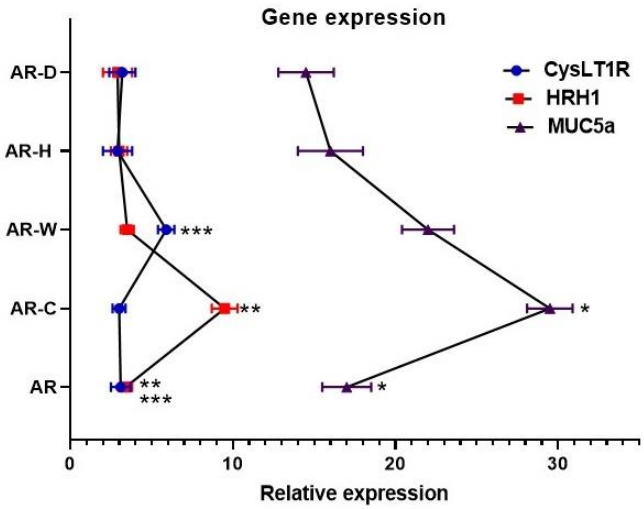

Figure 4. The expression of *MUC5a*, *HRH1*, and *CysLT1R* genes using real-time PCR between different groups of animals (standard (AR), dry (AR-D), humid (AR-H) [80±5% humidity], cold (AR-C), and warm (AR-W) [32±2°C]). Differences have been shown betwwen the test groups and standard group. *p<0.05, **p<0.01, ***p<0.001

DISCUSSION

As the airway gatekeeper, the nose filters, humidifies and warms the inhaled air (10,000 liters per day). Rhinitis is the inflammation of the nasal lining, and clinical symptoms include a runny nose, sneezing, itching, rhinorrhea, and obstruction.

Rhinitis is commonly caused by allergies (via IgE-mediated mast cell degranulation). Allergen avoidance is remarkably effective in AR patients, and immunotherapy is an effective treatment for AR. However, there are challenges with this treatment.[7-9]

AR can affect up to 50% of the pediatric population worldwide. The medications used for seasonal and perennial AR impact the quality of life. The available treatments for AR include antihistamines, intranasal corticosteroids, immunotherapy, and antileukotrienes. Antihistamines are the first line of therapy in AR. First-generation antihistamines are associated with adverse effects, such as sedation, caused by a lack of H1 receptor selectivity and drug penetration into the central nervous system. Second-generation antihistamines were developed with less frequent adverse effects.

Intranasal corticosteroid drugs can be absorbed through the airway epithelium and may suppress the hypothalamic–pituitary–adrenal axis. Montelukast is a leukotriene receptor antagonist that binds to the cysteinyl leukotriene receptor 1 with high affinity. Environmental factors such as weather conditions may affect the LTs.[10-12]

In this study, the AR group challenged with cold air conditions had increased histamine levels compared with the AR group in normal air conditions. Low temperatures stimulate histamine release and allergic reactions in the affected tissue, especially the mucosal and submucosal tissues of the airways.

AR has a 10% to 40% prevalence worldwide, affects many aspects of life, and remains a public health issue. Cold weather is associated with the development of AR, especially in boys, and extremely low temperatures trigger AR, especially in children. On the other hand, it has been estimated that 48% to 74% of the global population is affected by heat waves.[13,14]

Clinical, epidemiological, and biological evidence suggests that cold air affects respiratory symptoms and AR.[15] Inhalation of cold, dry air causes respiratory symptoms in the general population. Cold sensitivity in asthma has been confirmed in clinical provocation studies and during exercise tests in cold weather.[16,17] Wintertime cold temperatures are associated with higher rates of asthma exacerbations. Furthermore, lower temperatures exacerbate AR symptoms, which can have a negative impact on the quality of life for people with AR.[17] Shortness of breath in asthma patients with AR is affected by cold temperatures more severely compared to those with asthma alone. On the other hand, nasal mucosal drying could lead to hyperosmolality and bronchoconstriction. In dry air conditions, the mucosal tissue loses humidity and elasticity, which may irritate local nerves and cause clinical symptoms like sneezing.[16,17]

In this study, cold air and decreased temperature increased nose rubbing in AR mice. Furthermore, sneezing also increased in the AR mice kept in dry conditions. In cold conditions, the mucosal tissues of the nose and upper airways are irritated, and blood circulation may change, leading to clinical symptoms and nose rubbing. LTB4 and LTC4 levels were increased in the AR mice challenged by warm air conditions compared to the AR group without any challenge. Higher temperatures may trigger inflammatory factors, especially leukotriene-producing pathways such as the lipooxygenase cycle.

Hot, humid air causes immediate and transient bronchoconstriction. These changes are felt by the potential transient receptor type 1 vanilloid receptor (TRPV1), which is also expressed in the sensory nerve fibers of the pharynx, larynx, and upper airways. TRPV is a family of ion channels comprising 6 membrane domains that form non-selective and non-voltage cation channels. TRPV1-4 activation is affected by temperature.[18,19]

Some infections, such as *Linguatula serrata*, can change the expression of some related allergo-inflammatory molecules and immune responses that should be noted in infected environments, especially in endemic places.[20,21]

Total IgE and IL-4 levels did not change significantly in the AR-C, AR-W, AR-H, and AR-D groups compared to the AR group. *MUC5a* and *HRH1* genes were highly expressed in AR mice in cold air conditions compared with AR mice in standard air conditions.

Moreover, the *CysLT1R* gene was highly expressed in AR mice in warm air conditions compared with the AR mice in standard air conditions. Therefore, hot

weather conditions affect the production of leukotrienes and the expression of leukotriene receptors. On the other hand, cold weather conditions increase histamine secretion and histamine receptor expression. An increase in the *MUC5a* gene showed that cold temperatures could increase mucus production and secretion, which leads to excessive mucus secretion and nasal obstruction.

Finally, it was observed that air temperature and humidity affect AR's pathophysiology and can change AR's molecular pattern. Therefore, climatic conditions can be an essential factor in the control and treatment of AR and influence its future appearance. In future studies, we suggest that the effects of other environmental conditions, such as pollution (especially with heavy metals and newly synthesized chemical components), on the expression of related genes in AR should be studied. Also, it would be helpful to investigate the effect of weather conditions on AR pathophysiology in newborn, young, and older populations.

STATEMENT OF ETHICS

All methods, animal evaluation, and research ethics were approved by the Ethics Committee of the Laboratory Animal Moral Department of Veterinary Medicine (No: 2021VET.MED.ETHIC.A5690047).

FUNDING

The autthors received no financial support for this research.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGEMENTS

The authors have no acknowledgments to declare.

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